

Dr. Stanley

Friends of Dr. Avery; I came to the Rockefeller Institute in 1931, ~~and~~ ^{for} one year I had the great pleasure of walking the corridors of the Institute, having lunch and ^{as} just a raw, new Ph. D. ^{being} just a little bit starry-eyed with people like Landsteiner, Levine ^{and} Dr. Avery, as well ^{with} as some others who, because their interests were a little bit more diverse, I knew ~~them~~ less well. I then left and went down to Princeton, ^[There I] ~~and~~ had the good fortune ^{of} ~~there~~ becoming acquainted with and knowing Dr. Theobald Smith. So the Institute has given me an opportunity to be with and to remember and to walk with and to ~~eat with~~ dine with, some of the really greats, ~~and I think~~ Dr. Avery will stand high among ~~them~~ them. And this afternoon I am going to attempt to help you understand ^{and} perhaps it has helped me understand once again ^{why} a discovery which is literally one of the greatest discoveries of this century ~~and which~~ was fully understood ^[only] by the three men who made the discovery, ^[and why] the full significance of it ~~which~~ had so little impact on the rest of us at the time. I'll have to talk a little bit about nucleic acids, but I'd like to quote ~~out~~ from a paper that Dr. Bronk ^{mentioned}. This is the famous paper of 1944 ^{by} Avery, McCarty, MacLeod. ~~Just to~~ I shall have quite a few quotations, as a matter of fact, ~~to~~ to show the real conceptions and the misconceptions as they existed over the years with respect to this material, nucleic acid. ~~But anyway~~ ^{In} from their paper they stated: "highly polymerized nucleic acid must be regarded as possessing biological specificity, the chemical basis of which is as yet undetermined." Now that statement represented, I think, one of the landmarks in biological and the medical sciences. And it came just a little less than a hundred years after the discovery of the material that we now call nucleic acid by ^{Miescher} ~~Miescher~~ in 1869, working initially with pus cells and then later on

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with the heads of salmon sperm. ^{MIESCHER}~~Miescher~~ identified the material reasonably well chemically; he understood the fact that there was a type of assault between nucleic acid and the protein material of protein, and he did some really remarkable chemistry, ~~and~~ ^{and} for about 30 years, the chemistry of nucleic acids was very good, and this includes the beginning of the work here at The Rockefeller Institute by ^{PHOSPHORUS} ~~E. A.~~ ^{P. A.} Lev^Ene. Lev^Ene, I think, came to The Institute in 1907, but had been working here in New York City on nucleic acid since 1901. The structural organic chemistry which was done over those years, beginning with ^{MIESCHER}~~Miescher~~'s more biological work and through the work of Lev^Ene and Jones at Hopkins, was top-flight organic chemistry. And you would have thought that it would have worked out very well. The biologists became interested in nucleic acid quite early, and here I would like to quote from a book written by E. B. Wilson just at the turn of the century, when he wrote that chromatin, ~~this is~~ a nucleic acid material, is known to be closely similar to, if not identical with, a substance known as nucle^{IN}~~in~~, which analysis shows to be a tolerably definite chemical compound composed of nucleic acid and albumin. ^{REACHED}~~reach~~ ^{us} thus we ~~reach~~ the remarkable conclusion that inheritance may perhaps be affected by the physical transmission of a particular chemical compound from parent to offspring. ~~You~~ ^{you} contrast this with the strictly chemical work, where the relationship to biological specificity did not occur, apparently, to the chemists, ~~and~~ yet the biologists of those years, ^{beginning} ~~in~~ 1895 and continuing on with increasing fervor for about 20 years, ~~they~~ re-expressed this ~~the~~ general idea that nucleic acid had to have something to do with genetics. And then came, what, to me, is one of the most remarkable turn-arounds in ~~science, in~~ medical science. ~~And~~ I can again quote from E. B. Wilson ~~again~~ in his book, The Cell, which he wrote in 1925. He said, "Apart from the characteristic differences between animals and plants, the nucleic acids

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of the nucleus are on the whole remarkably uniform^{as} [as the two preceding speakers have already indicated],^{showing} showing with present methods of analysis no differences in any degree commensurate with those from the various species of cells from which they are derived. In this respect, they show a remarkable contrast to the proteins, which, whether simple or compound, seem to be of an inexhaustible variety. It has been suggested accordingly that the differences between different chromatⁱns depend upon their basic or protein components and not upon their nucleic acids." This^{is} ~~just~~ diametrically opposed to what Dr. Wilson apparently thought and wrote 30 years earlier. ~~What~~ can we explain this? Well, I think we can. And, being a chemist, perhaps I'm in a better position to attempt to explain it than^{is} a biologist. I think that it was due to the really great chemistry of a colleague of mine here at The Rockefeller Institute, and this is P. A. Lev^ene. Lev^ene was one of a very small number of people who did excellent work on structural nucleic acid chemistry. ~~After~~ ^{Miescher} after ~~Miescher~~ there was Posel, then Lev^ene and Jones, and they had very few colleagues, so all of the work on nucleic acid^{was} ~~was~~ in the hands of a very, very small number of people. ~~What~~ Lev^ene was the leading proponent of ~~the~~ the tetranucleotide theory of the structure of nucleic acids; in other words, that it's composed of four building blocks ^{that} and these ~~are~~ ^{are} repeated over and over again. I can quote, ~~perhaps~~ to try and give you a little bit of the flavor of the time, from a book which Dr. Lev^ene wrote with Bass in 1931. On page 276, for example, it's written: "thus the tetranucleotide structure of yeast nucleic acid has been reestablished by the analytical method. It will be seen later that the formulation of Lev^ene has been confirmed by the physical chemical method." ~~and then~~ on page 289, they state, with some reservations now, about the structure: "On the other hand, it must be born^e in mind that the true molecular weight of the nucleic acids

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is as yet unknown. The tetranucleotide theory is the minimum molecular weight and the nucleic acid may well be a multiple of it. You see, there is still no idea of biological specificity. They're thinking just about four things tied ^{together} over and over again in a monotonous polymer. ~~Was~~ this, I think, was the feeling of the times. ^{As} ~~I think~~ Dr. McCarty ^{and} Dr. MacLeod have already indicated, when they began ^{to} ~~the~~ work on the transforming principle, ~~and~~ it was a very different and a very difficult scientific atmosphere. I can well remember those days, because, as Dr. McCarty has already indicated, I was interested in this phenomenon from the standpoint of the possibility that they might have a bacterial virus. ~~and~~ I remember writing in those days, 1937, this was: "it is obvious that there is a factor which may be obtained from any one of the S-type organisms that is normally absent from the type-R cells, but when added to such cells induces their conversion into the same type of S organisms in which the factor was derived, with the very important result that more of the factor is produced in the induced S cells. Then I state: "this phenomenon is virus-like, and it is because of this and the fact that it may become important from the standpoint of the chemistry of viruses that a discussion of it is included here. ~~and~~ then I went ahead with the same sort of story that has already been presented to you, and ended up by: "no chemical tests at that time had been made, hence nothing is known about the nature of the active agent. It is to be hoped that the study of this agent will be continued because of its virus-like nature." Well, as you well know, within a very few years after that, the three scientists did obtain definite information concerning the fact that it was deoxyribonucleic acid. ~~Well~~ you would have thought ^{/-/} and I must say reminiscing can be very damaging to your ego ^{/-/} you would have thought that with this and my knowing about it in 1944, and having obtained tobacco mosaic virus as a nuclear protein a few

years earlier, ~~that~~ this would have impressed me tremendously. ~~and~~ I have delved deep into my brain to try and explain why it didn't. I don't know whether it was because tobacco mosaic virus had RNA in it instead of DNA, but DNA was supposed^d to be the genetic material and RNA was thrown over to one side as being different. I sometimes wonder if, because the war came on at this particular time, we dropped all of our fundamental work and went into the work for the Armed Forces, ~~but~~ in any case, it is a sad commentary on my own intelligence that this did not have the effect that it should have had in 1944 and ~~the~~ ^{for} years after that. ~~And~~ I simply cannot explain it, except that I am in a company of a few other people who took almost ten years before the significance of this ~~discovery~~, really remarkable discovery_x was fully recognized. It took, in my own case, the isolation of tobacco mosaic-virus nucleic acid, and the proof that this RNA had biological activity, to really shake me up ^[force me to] and go back and realize how fully I had been missing a real pearl, which was right here at The Rockefeller Institute over these many years.

You see even the work of Alexander and Lidy on the transforming of the influenza^A bacillus still didn't shake up the scientific world very much. ~~and~~ the work later of Hershey and Chase, which was as late, I think, as 1952, ^{and} the work that Hotchkiss did here, started the rumbling that finally resulted in ~~the beginning~~ the beginning of the recognition that should have come ~~I think~~ many years before. There was the discovery by Lederberg and Zinder of the transduction phenomenon, which was even before the isolation of tobacco mosaic-virus nucleic acid. But then ~~there has been~~ a literal revolution ^[has] ~~that's~~ taken place in the last 15 to 18 years. ~~I think~~ there's been ^{an} ~~that~~ accumulation of a half, ^{almost} three-quarters, of a century of welling up of information, ~~and~~ at long last, sorting things out the way they belong, ~~that~~ scientists have finally realized the great significance of the 1944 discovery. This ~~has~~ now, ~~with~~ with tremendous work in molecular biology, is one of

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the most active fields in all of science. I think also it is one of the fields of greatest potential benefit for mankind, ^[all] ~~with the more~~ ^[more] we learn about the tremendous information which can be wrapped up in nucleic acid in the way of genetic material. As has been stated, ~~I think~~ perhaps by one of the members here at The Institute, there is the potential ~~of course~~ eventually of controlling the messages that are contained in nucleic acid, and I think you may learn from Dr. Holley in just a moment or two about some of the progress that has been made ~~in the structure work~~ in elucidating the structure of the nucleic acids. ~~Now in the case the impact finally did happen to the virus field~~ there has been, in the last 6 or 7 years, a tremendous amount of excellent work on viral nucleic acids and, as you probably know, quite a number of the viral nucleic acids have been isolated in pure form. [—] it has been discovered, first in ^{SINSHIMER'S} ~~Zinck~~ laboratory and then again in Ochoa's laboratory here in collaboration with our laboratory, [—] that nucleic acid, be it RNA or DNA, can act as genetic material; that when it is reproduced, it can form a helical double structure in a ring-type form, which, from the standpoint of nature, makes it a beautiful way to reproduce its own kind. you put a little ^{polymerase} ~~proliferase~~ molecule on the ring and it can run right around and read off all of the messages you see ~~there~~ there. In the case of these viral nucleic acids, they themselves are the messengers, ^[y] ~~in case~~ you are familiar with the current dogma with respect to DNA, RNA, and protein. ~~All of this I think~~ [—] now we can go back to this discovery of Avery, MacLeod, and McCarty in 1944, ~~and I think now that scientists throughout the world, and~~ if you read the scientific literature as it exists today, you will see that this tremendous discovery is receiving, at long last, the recognition that it truly deserves. The impact comes slowly sometimes, but it comes with resounding force when it does happen. I appreciate very much the chance to come back and, in some small way, participate in this tribute to Dr. Avery. I never worked with him, but he was one of the greats ^[Luhman] ~~that~~ I liked to brush close to as I walked the halls here in 1931. Thank you.

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